

Interpretation bias in the face of pain

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Original experimental

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Interpretation bias in the face of pain: a discriminatory fear conditioning approach

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Abstract

Background and aims: Interpreting pain- and illness-related stimuli as health-threatening is common among chronic pain patients but also occurs in the general population. As interpretation bias (IB) may affect pain perception and might even play part in the development and maintenance of chronic pain, it is important to improve our understanding of this concept. Several studies suggest an association between IB and pain-related anxiety. However, those studies often rely on verbal and pictorial IB tasks that do not entail a threat of actual pain, therefore lacking personal relevance for healthy participants. The current study investigated whether healthy individuals show an IB towards ambiguous health-related stimuli in a context of actual pain threat, and explored whether this bias is associated to pain anxiety constructs.

Methods: Thirty-six healthy participants were conditioned to expect painful electrocutaneous shocks (unconditioned stimulus – US) after health-threat words (CS+) but not after neutral (non-health-threat) words (CS–) in order to establish fear of pain. Subsequently, they completed a verbal interpretation task that contained new CS+ and CS– stimuli as well as ambiguous non-reinforced health-threat and non-health-threat words. IB was assessed through shock expectancy ratings and startle responses to ambiguous and evident health threatening or

neutral word stimuli. Pain-related anxiety was measured with validated questionnaires.

Results: The results show a general IB towards ambiguous health-related words on pain expectancies but not on startle response. An exploratory analysis suggests that this effect exists irrespective of pain-related anxiety levels which however may be due to a lack of power.

Conclusion: We present a novel experimental paradigm employing actual health threat that captures IB towards health-related stimuli in healthy individuals. Taken together, results provide evidence for the further consideration of IB as a latent vulnerability factor in the onset and maintenance of pain chronicity. In contrast to previous studies employing a safe, pain-free context, we found that healthy participants show an IB towards ambiguous health-related stimuli, when confronted with pain threat.

Implications: Like chronic pain patients, healthy individuals display an IB towards health-threat stimuli when these stimuli become personally relevant by carrying information about pending health threat. Therefore, the presented paradigm could be valuable for pain-related cognitive bias research in healthy participants as it may have a higher ecological validity than previous study designs. Future studies will have to elucidate the influence of anxiety constructs on IB in larger samples.

Keywords: interpretation bias; pain threat; acute pain; startle response; pain expectancy.

1 Introduction

Understanding cognitive bias for pain and health threat – i.e. being easily drawn to and remembering pain- and illness-related information as well as having the tendency to interpret ambiguous information as health-threatening – is pivotal to the understanding of pain and pain-related distress as they are likely to affect pain perception [1] and are conceptualized as latent vulnerability mechanisms within the onset, maintenance, and exacerbation of chronic pain complaints [2, 3]. A growing body of evidence suggests that interpretation bias (IB) for pain/health-threat stimuli,

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which can be defined as “an excessive and/or inappropriate generation of threat meaning assignment in response to stimuli or situations that are innocuous” [4], depends on pain-related anxiety. Indeed, fear of pain, pain catastrophizing (PC), illness/injury sensitivity (IS) and anxiety sensitivity (IS) were frequently reported to correlate with IB in both pain patients [5, 6] and healthy participants [1, 7, 8]. However, inconsistency in occurrence and strength of these associations in healthy samples [9, 10] instigates closer investigation of this association.

Previous experiments have typically assessed pain-related IB for ambiguous verbal or pictorial stimuli that are semantically associated with pain-threat; e.g. word stem completion tasks, ambiguous word priming task, and incidental learning paradigms (for a systematic review of these paradigms see [11]). Results of these studies offered valuable insights into IB for abstract information matching the content of pain-related concerns, schemata, and memory. However, the absence of actual (imminent) painful stimuli in these paradigms reduce their ecological validity and hamper firm conclusions regarding the hypothesized occurrence of IB in an ambiguous context that holds direct threat of pain, especially in nonclinical samples.

To overcome this caveat in the literature, the present study adopts a classical fear conditioning paradigm to examine IB towards health-threat words in healthy participants under actual pain-threat as signaled by word stimuli. In a first phase of the study, words with a clear health threat content (the conditioned stimulus, CS+; e.g. “pain”) were paired with painful electrocutaneous stimulation (ES) (the unconditioned stimulus, US) and words that were clearly unrelated to health threat (CS–; e.g. “island”) with the absence of the US. Thus, health threat words acquired informational value about the occurrence of the ES, making them a warning signal and personally relevant. In a second phase, participants viewed ambiguous (e.g. “lame”, “bank”) and unambiguous words; half of them were related to health threat. In this phase, startle responses as well as ES expectancy ratings were assessed for all words. Doing so, IB could be derived from implicit (indirect) startle responses as well as explicit (direct) expectancy ratings. This approach aims to overcome problems inherently bound to other paradigms in which IB is inferred from a direct interpretation of verbal ambiguity or reaction latencies to threat-irrelevant task features, like social desirability, literacy, motor responses, or executive functioning [12].

It was hypothesized that ES expectancies and startle responses would be augmented for unambiguous health threat words that signal painful ES as compared

to unambiguous non-threat words that signal safety. Crucially, increased ES expectancy ratings and startle responses to ambiguous health threat words indicate negative IB with selective access to the threat meaning of the ambiguous words. In addition, the relation between IB, fear of pain, ES experience ratings, and pain anxiety constructs is explored.

2 Methods

2.1 Participants

Sample size was based on a priori power analyses (G*Power [13]) for the main effects of word type (HT, NHT, AHT, ANHT) in acquisition (conditioning effect) and test phase (IB) of the IB paradigm, and indicated that a minimum of 20 participants were needed to detect medium effect size at 80% power and $p < 0.05$. Thirty-six healthy Dutch students (29 females) from Maastricht University aged 19–44 years ($M = 22.36$, $SD = 4.63$) participated in this study. Participants were recruited through posters at Maastricht University and through the university’s online participant recruitment system, SONA. Inclusion criteria assessed by means of self-report consisted of being in good health, i.e. no diagnosis of current psychopathology and not suffering from acute or chronic (> 3 months) pain. People were not eligible if their mother tongue was other than Dutch or if they were dyslexic as this could have posed difficulties with the verbal interpretation task. Furthermore, due to the usage of electrocutaneous stimuli exclusion criteria constituted pregnancy and history of cardiovascular diseases. Written informed consent was obtained from each participant at the beginning of the experiment. Participation was rewarded with either one course credit or financial compensation in the form of a VVV-coupon worth €7.50. The study protocol was approved by the local Ethics Committee of the Faculty of Psychology and Neuroscience of Maastricht University (ERCPN) and adhered to the standards of the Declaration of Helsinki.

2.2 Measures

2.2.1 Interpretation paradigm

Word stimuli. An ambiguous words task using homographs, i.e. words with identical spelling but distinct meaning, was used for the interpretation paradigm [11].

Word stimuli were Dutch words from four different categories [9, 14]: health threat (HT, e.g. “death”), non-health threat (NHT, “pencil”), ambiguous health threat (AHT, e.g. “temperature”) and ambiguous non-health threat (ANHT, e.g. “pool”). The two non-ambiguous categories consisted of 16 words each while the ambiguous categories contained eight words, respectively (see Appendix for a list of stimulus words and their English translation).

AHT words were selected on the basis of a word pilot study. For each of 58 word stimuli (29 AHT, 15 NHT and 14 ANHT word-stimuli) 20 volunteers wrote down the first association that came to their mind. Two independent raters scored these answers either as a “health-related interpretation” or a “non-health related interpretation”. Ideally, an AHT stimulus should be interpreted as health-related by 50% of the sample. The stimuli that came closest to this distribution (health-threat vs. non-health threat related interpretations: $2 \times 48\% - 52\%$; $2 \times 43\% - 57\%$; $4 \times 62\% - 38\%$) were selected for the interpretation task.

2.2.1.1 Painful electrocutaneous stimulation

Pain was induced through sinus wave electrocutaneous shocks (100 ms duration, 50 Hz, Bipolar sinus waveform) that were administered through two Ag/AgCL-electrodes attached to the backside of the non-dominant forearm, with an interelectrode distance of 1 cm. Before applying the electrodes, in order to reduce skin resistance participants scrubbed their own skin with a commercial scrub cream, and the electrodes were filled with electroconductive gel (K-Y gel, Johnson & Johnson). Currents were delivered by an isolated bipolar current stimulator (DS 5, Digitimer Ltd., Welwyn Garden City, England).

The intensity of the ES was determined individually, using a calibration procedure (c.f. [15] with gradually increasing shock intensity in fixed steps of 0.5 mA. After each stimulus participants decided whether they were able to tolerate that intensity and whether or not they wanted to try the next step. Once this rating was provided, the experimenter presented the next stimulus intensity. The series was ended when the participant indicated that tolerance was reached or when the pre-set maximal intensity of 10 mA was reached. This procedure was repeated three times; the highest intensity of the second and third series of ES was used in the acquisition and test phases of the interpretation task. Mean intensity used in the experiment was 3.06 mA (SD = 1.67, range = 0.50–6.50).

2.2.1.2 Interpretation bias paradigm

The task was programmed in E-prime (Psychology Software Tools, Inc., 2012), run on a Dell optiplex 755 computer and presented on a 19-inch Samsung Syncmaster 931 BF LCD monitor (1,920 × 1,080 resolution). The interpretation task followed a discriminatory fear conditioning paradigm with an acquisition and a test phase (see Figure 1 for an illustration of the task design).

In the acquisition phase, eight HT and eight NHT words were presented once in each of two blocks in random order with no more than two words of the same category in a row, with the first stimulus being an NHT and the last one an HT word. Each word was centrally presented on a computer screen for 4,000 ms [16] with inter-trial intervals (ITI) of 3,000, 3,300, 3,700 or 4,000 ms (randomly distributed over acquisition and test phase with restriction that each ITI occurs equally often in each phase,

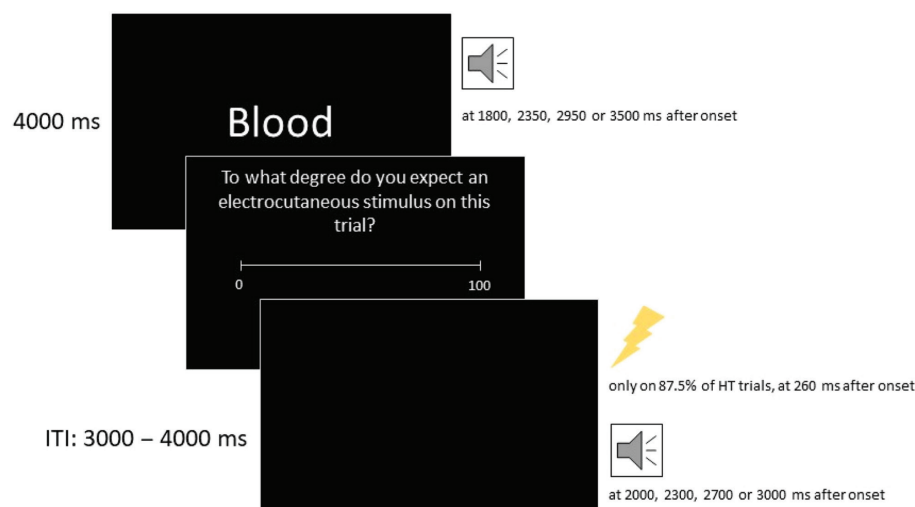


Figure 1: Overview of the experimental procedure.

i.e. eight times). The HT words were followed by a painful ES (260 ms after onset of the ITI) on 87.5% of the trials while the NHT words were never followed by ES. This way, HT words were classically conditioned to become CS+ and NHT words became CS− (for an illustration of the trial configuration see Figure 2).

The test phase was similar to the acquisition phase except that 8 HT, 8 NHT, 8 AHT, and 8 ANHT words were presented once each. From the HT and NHT categories, only words were presented that had not already been presented in the acquisition phase. Again, only the HT word trials were followed by ES (contingency: 87.5%) whereas none of the other categories was ever paired with a shock.

2.2.1.3 Shock expectancy ratings

Participants indicated the degree to which they expected the ES to occur on a 100 mm Visual Analogue Scale (VAS) with the anchors “certainly no ES” (0) and “certainly an ES” (100). Expectancy ratings in the acquisition phase served as a measure for the success of the classical conditioning procedure. Expectancy ratings in the test phase served as an index of IB.

2.2.1.4 Startle responses

The startle response is a non-invasive measure of activation of the central nervous system and contains, among others, the eyeblink reflex [17]. It has been frequently used as an indicator of fear learning in several experiments related to classical conditioning and pain [18, 19] as well as IB for ambiguous (threat) stimuli [20, 21].

Eyeblink reflexes were measured with surface electromyography (EMG) recordings. One electrode was placed on the skin on top of the circular eye muscle (orbicularis oculi) centrally underneath the right eye, a second electrode was attached 1–2 cm lateral to the first electrode, and a ground electrode was attached behind the right ear following the guidelines on human startle eyeblink EMG [17]. An acoustic startle probe (white noise,

95 dB, instantaneous rise and fall, duration 50 ms) was presented through a headphone during the interpretation task both during word-stimulus presentation (either 1,800 ms, 2,350 ms, 2,950 ms or 3,500 ms after stimulus onset) and ITI's (1,000 ms before end of ITI, hence at 2,000 ms, 2,300 ms, 2,700 ms, or 3,000 ms after ITI onset).

2.2.2 Self-report measures

2.2.2.1 Fear of Pain Questionnaire – Short Form (FPQ-SF)

Fear of pain was assessed using the Dutch version of the FPQ-SF which was derived from FPQ-III [22]. Participants rate their level of fear for 20 different situations (e.g. “Being in an automobile accident”) on a five-point Likert scale (1 = not at all fearful; 5 = extremely fearful). The Dutch version of the FPQ has good psychometric properties [23].

2.2.2.2 Pain Catastrophizing Scale (PCS)

The PCS is a 13-item questionnaire that measures catastrophic thoughts and feelings regarding perceptions of pain across three different factors, i.e. rumination, magnification, and helplessness [24, 25]. Participants indicate on a five-point Likert scale ranging from 0 = “not at all” to 4 = “always” to what extent the statements, such as “I become afraid that the pain may get worse”, apply to them. Higher scores reflect more catastrophic thinking. The psychometric properties of this instrument are good [26].

2.2.2.3 Anxiety Sensitivity Index (ASI)

The Dutch version of the ASI was used to measure anxiety sensitivity [27]. The 16 items rated on a five-point Likert scale (1 = strongly disagree; 5 = strongly agree) assess beliefs about negative consequences from experiencing anxiety in social and somatic domains, the latter of which is assumed to be relevant in the field of pain [28]. The ASI has a good internal consistency ($\alpha = 0.88$) [29].

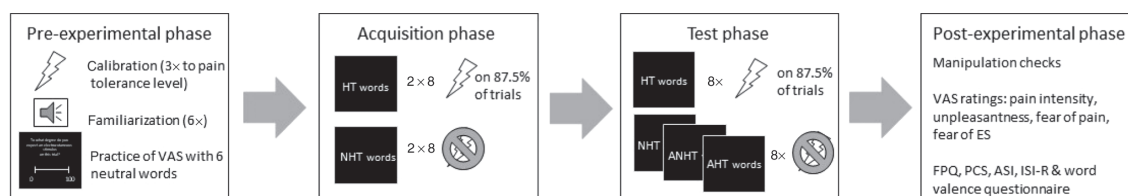


Figure 2: Trial configuration for both the acquisition and test phase in the interpretation task. After word presentation (4,000 ms) participants indicate the extent to which they expect occurrence of the electrical stimulation (ES) on a 0–100 VAS. Startle probes are presented at either 1,800 ms, 2,350 ms, 2,950 ms, or 3,500 ms after word onset; and again at 2,000 ms, 2,300 ms, 2,700 ms, or 3,000 ms after onset of the inter-trial interval (ITI: 3,000 or 4,000 ms). An ES is presented following 87.5% of all non-ambiguous health threat (NAHT) words.

2.2.2.4 Injury/Illness Sensitivity Index-Revised (ISI-R)

Fear of injury and illness was measured by means of the ISI-R [30, 31]. This instrument consists of two subscales: injury (five items) and illness (four items). Participants indicate to what degree they agree with each of the nine statements (e.g. “I worry about being injured”) on a five-point Likert scale ranging from 0 (agree very little) to 4 (agree very much). The ISI-R has satisfactory psychometric properties in general [31].

Internal consistencies for the four questionnaires in the present sample are shown in Table 2.

2.2.2.5 Pain experience ratings

Pain intensity, pain unpleasantness, fear of ES and fear of pain caused by the ES were assessed on 100 mm VAS, labeled 0 (not at all painful/unpleasant/fearful) at one extreme and 100 (extremely painful/unpleasant/fearful) at the other extreme.

2.2.3 Contingency awareness check

In order to test whether participants were aware of the shock contingency and of the research purpose they were asked: (1) if they had noticed anything regarding the types of words and if so, what they noticed and whether it affected their responses; (2) if they had noticed different categories of words and if so, how they would label these categories; and (3) if they had noticed anything about the occurrence of ES.

2.3 Procedure

An overview of the experimental procedure is presented in Figure 1. Upon receiving written information about procedural aspects of the experiment and the opportunity to ask questions, participants provided informed consent. The skin underneath the right eye, behind the right ear and on the backside of the non-dominant forearm was scrubbed and cleaned to reduce resistance. The two startle electrodes, the ground electrode, and the two Ag/AgCl-electrodes were attached to the respective locations. Participants were seated ~60 cm in front of a computer screen.

In the pre-experimental phase, the intensity of the ES was individually calibrated to pain tolerance level. Next, the startle sound was presented six times to familiarize participants with the characteristics of the sound. Furthermore, participants practiced the use of the ES expectancy VAS for the interpretation task by indicating their shock

expectancy for six neutral words (other words than during experimental task) without actual shocks being delivered.

Subsequently, participants completed the interpretation task (see Figure 2). They were instructed to find different types of words that would help them to predict the ES (“If you pay attention to the different types of words, you will be able to predict more adequately”) to maximize contingency awareness and classical conditioning effects. Participants next completed the manipulation check questions, the retrospective VAS ratings regarding pain intensity, unpleasantness, fear of pain and fear of electric shock, as well as the four pain anxiety questionnaires (FPQ, PCS, ASI, ISI-R). For other study purposes, participants next completed some questionnaires and a valence rating for a list of words; these measures are not considered further in the present study. Study participation took around 30 min.

2.4 Data Reduction and Statistical Analysis

Startle response EMG data were analyzed offline using Brain Vision Analyzer software (v. 2.0 Brain Products, Gilching, Germany) following the procedure of Andreatta et al. [32]. Data were filtered (low cut-off filter 28 Hz, high cut-off filter 500 Hz, moving average of 50 ms) and rectified. Peak amplitudes defined as the maximum of the response curve within 20–150 ms after the startle probe onset relative to baseline (mean EMG activity over 50 ms preceding startle probe onset) were calculated for each trial (see [33]). In order to normalize data and to reduce inter-individual variability that is not related to psychological processes, startle response amplitudes were standardized as z-scores per person across all trials [17]. Per word category, average startle scores were then calculated as the difference score between the average of the word trials belonging to each category and average ITI startle scores.

Data were analyzed using SPSS 21.0 [34]. Means and standard deviations were requested for all measures, and data were checked for normality, outliers and missing values. Contingency awareness was derived from open questions and evaluated manually. In order to check whether conditioning was successful, two 2 (type: HT vs. NHT) \times 2 (stimulus presentation block: first vs. second) repeated measures ANOVAs were conducted, respectively on startle responses and shock expectancies during acquisition.

Two repeated measures ANOVAs examined the effect of word type (HT/NHT/AHT/ANHT) on startle responses

and shock expectancies during test phase. Main effects were followed up with pairwise comparisons, adjusted for Bonferroni. Next, two IB indexes, IB_{ratings} and IB_{startle} were calculated as the difference score between mean AHT and mean ANHT for ES expectancies and startle responses, respectively, such that positive IB scores are indicative of IB towards health threat. The relation between both IB indexes and fear of pain, pain experience ratings, and pain anxiety constructs was explored with Pearson correlation coefficients which were Bonferroni-corrected in order to control for multiple testing. For repeated measures ANOVA, generalized eta-squared (η_g^2) was calculated to obtain a measure of effect size [35]. For follow up analyses (t -tests), confidence intervals (CI) of the mean difference and partial eta squared (η_p^2) were calculated and reported [36].

3 Results

3.1 Contingency awareness

On the contingency awareness scale all participants but one were able to identify word categories upon request, and all but four participants correctly reported the association between the “negative”/“medical”/“health-related” words and the ES. Hence, 32 participants were classified as contingency-aware. As the importance of awareness for learning has been emphasized [37], all analyses were performed on the aware subsample.

3.2 Interpretation task

3.2.1 Acquisition phase

The repeated measures ANOVA on shock expectancies revealed significant main effects for word type ($F(1,31)=618.53, p<0.001; \eta_g^2=0.94, 95\% \text{ CI}=[61.20; 72.13]$) indicating higher expectancies for HT than for NHT. Furthermore, this difference increased over time as indicated by a significant effect of presentation block ($F(1,31)=14.18, p=0.001; \eta_g^2=0.21, 95\% \text{ CI}=[-6.48; -1.93]$) as well as a significant word type \times presentation block interaction ($F(1,31)=51.53, p<0.001; \eta_g^2=0.13$). Bonferroni-corrected follow-up pairwise comparisons showed an increase in shock expectancies for HT words from first presentation ($M=66.74, SD=14.01; t=26.95, p<0.001; 95\% \text{ CI}=[61.69; 71.79]$) to second presentation block ($M=80.92, SD=13.25; t=34.54, p<0.001; 95\% \text{ CI}=[76.14; 85.69]$),

and a decrease in shock expectancies for NHT words from first ($M=10.17, SD=8.21; t=0.01, p<0.001; 95\% \text{ CI}=[7.21; 13.123]$) to second presentation block ($M=4.40, SD=3.978; t=6.26, p<0.001; 95\% \text{ CI}=[2.97; 5.84]$).

With regard to startle responses, the main effect of word type approached significance ($F(1,31)=3.95, p=0.056; \eta_g^2=0.05, 95\% \text{ CI}=[-0.33; 0.004]$) with more pronounced startle responses at HT word trials ($M=0.16, SD=0.53$) compared to NHT word trials ($M=-0.004, SD=0.31$). Again, a main effect of presentation block was observed ($F(1,31)=30.47, p<0.001; \eta_g^2=0.44, 95\% \text{ CI}=[0.284; 0.616]$), with startle amplitudes decreasing from block 1 ($M=0.43, SD=0.43$) to block 2 ($M=-0.02, SD=0.43$). No interaction effect was found ($F(1,31)=0.28, p=0.604; \eta_g^2=0.001$).

3.2.2 Test phase

The repeated measures ANOVA on shock expectancies (Figure 3) revealed a significant main effect for word type ($F(3,29)=245.45, p<0.001; \eta_g^2=0.92$) with the greatest expectancies for HT words ($M=79.25, SD=13.35$), followed by AHT words ($M=41.66, SD=15.21$), and equally low expectancies for NHT ($M=5.21, SD=5.14$) and ANHT words ($M=5.67, SD=5.54$).

The repeated measures ANOVA on startle response (Figure 4) revealed a significant main effect for word type ($F(3,29)=5.18, p=0.005; \eta_g^2=0.11$) with the most pronounced startle for HT words ($M=0.14, SD=0.50$) which differed significantly only from NHT words ($M=-0.13, SD=0.31$) as indicated by pairwise comparisons ($p=0.005$;

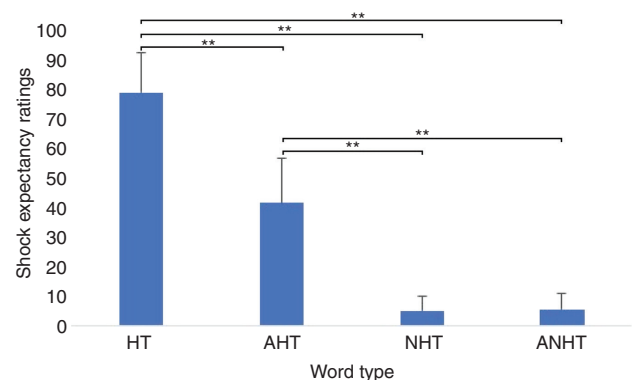


Figure 3: Shock expectancy ratings (mean, standard deviation bars) for each Word Type in the test phase of the interpretation task. Word Types: health threat (HT), non health threat (NHT), ambiguous health threat (AHT) and ambiguous non health threat (ANHT) words. **Indicates a statistically significant difference between Word Type categories ($p<0.01$).

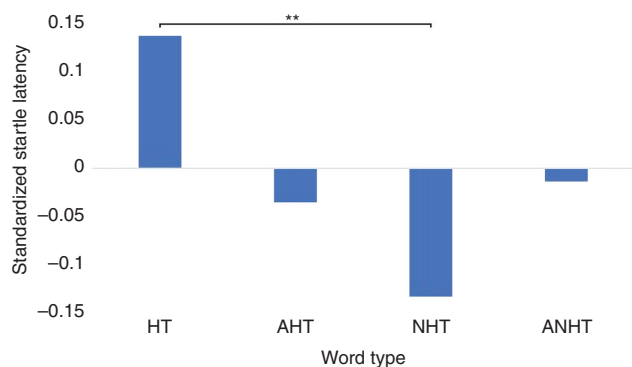


Figure 4: Standardized startle latencies (mean) per word type in the test phase of the interpretation task. Word Types: health threat (HT), non health threat (NHT), ambiguous health threat (AHT) and ambiguous non health threat (ANHT) words. **Indicates a statistically significant difference between Word Type categories ($p < 0.01$).

95% CI = $[-0.47; -0.06]$. There were no significant differences between any of the other word types.

3.3 IB index, pain reports, and pain anxiety

Mean $IB_{expectancies}$ was 35.98 (SD = 14.97) and Mean $IB_{startle}$ was -0.05 (SD = 0.34). Both IB indexes did not correlate significantly with one another, with $r(32) = 0.29$, $p = 0.10$.

Five participants did not fill in the pain experience ratings. Descriptives for the four VAS ratings of the remaining 27 participants and their correlations with $IB_{expectancies}$ and $IB_{startle}$ are presented in Table 1. Pain unpleasantness ratings and fear of the ES were found to be marginally positively associated to $IB_{expectancies}$ ($r = 0.35$, $p = 0.074$ and $r = 0.37$, $p = 0.055$, respectively). Specifically, this seemed to be driven by correlations with ES expectancies for AHT words (fear of ES: $r = 0.474$, $p = 0.012$; pain unpleasantness: $r = 0.377$, $p = 0.052$) whereas none of the other types of word stimuli were correlated with pain unpleasantness or fear of the ES.

The scores on the PCS, ASI, ISI-R, and FPQ can be found in Table 2. Participants' scores on PCS and FPQ were lower than the norm scores from healthy university students [9, 38–40] while those for ASI were higher than those obtained by Vancleef et al. [9] ($M = 10.87$, $SD = 5.93$; range: 3–29). ISI-R scores [9, 41] were comparable to scores as observed in healthy student samples (Vancleef et al. [9]: $M = 7.60$, $SD = 5.8$; range: 0–29). There were no significant correlations between both IB indexes and pain anxiety constructs (PCS, FPQ, ASI, and ISI-R).

4 Discussion

The present study aimed to investigate IB towards ambiguous health-related words in healthy participants under actual pain threat. To this end, we followed a fear conditioning procedure during which participants first successfully learned associations between health threat words and painful ES, and between non-health words and safety as indicated by higher expectancy ratings as well as trend-wise more pronounced startle responses for HT than for NHT words during acquisition. During the following test phase, IB was inferred from expectancy ratings and startle responses to ambiguous health threat words compared to ambiguous non-health threat words.

The results show a clear IB on expectancy ratings, thereby supporting previous studies suggesting an IB for health-threat stimuli in healthy people [1, 7, 9, 10, 42] and even extend these findings to a context of actual pain threat. However, no such effects were found with regard to startle response: startle latencies were generally increased for HT stimuli but did not differ between the other categories. None of the IB-indexes correlated significantly with subjective ratings of the ES. Given that self-reports and startle responses frequently do not match [32], this inconsistency might not be surprising. According to the dual-process theory self-reports and ratings stem from an explicit knowledge system whereas startle response and

Table 1: Means and standard deviations for the pain and shock 0–100 VAS ratings and correlations with both IB indexes ($n = 27$).

	Mean	SD	Range (min, max)	Correlations (p -Value)	
				$IB_{expectancies}$	$IB_{startle}$
Pain intensity	46.50	18.96	11.5–79.5	0.11 (0.580)	-0.27 (0.167)
Pain unpleasantness	62.35	18.56	14.0–91.0	0.35 (0.074) ^a	-0.08 (0.692)
Fear of ES	35.13	27.15	0–98.0	0.37 (0.055) ^a	-0.21 (0.290)
Fear of pain from ES	32.17	27.95	1.0–97.0	0.18 (0.359)	-0.27 (0.169)

ES = electrocutaneous stimulus.

^a $p \leq 0.10$.

Table 2: Means, standard deviations and Cronbach's α of the questionnaires and correlations with IB_{expectancies} and IB_{startle} ($n = 32$).

	Mean	SD	Range (min, max)	Cronbach's α	Correlations (p -value)	
					IB _{expectancies}	IB _{startle}
FPQ	46.72	10.54	30–80	0.88	0.09	0.27
PCS	12.44	7.24	4–34	0.89	–0.12	0.15
ASI	26.34	4.32	20–39	0.69	–0.12	0.02
ISI-R	7.94	6.04	0–25	0.90	–0.07	0.14

IB = interpretation bias; FPQ = Fear of Pain Questionnaire – short form; PCS = Pain Catastrophizing Scale; ASI = Anxiety Sensitivity Index; ISI-R = Injury/Illness Sensitivity Index-Revised (ISI-R).

other physiological reactions belong to a more impulsive, implicit system, and these two systems may act independently from another [43–45].

Furthermore, exploratory analyses indicate that in contrast to other studies [1, 7–9, 42], IB was not associated to individual levels of pain anxiety in the present experiment. It needs to be noted that our sample was underpowered to detect effects of pain anxiety constructs, so this difference might be explained by the lack of power. Future studies with larger samples will have to elucidate whether this is a robust finding. If so, such a deviation could be explained by the fact that we created a situation of actual pain threat within which threat level was controlled by adjusting the ES to each individual's pain tolerance. Hence, when acute health threat is present, even healthy people may be inclined to make negative interpretations in ambiguous situations within the health domain, irrespective of trait anxiety levels [2]. According to cognitive models of anxiety [46, 47], there is an evolutionary benefit to prioritizing and negatively interpreting severely threatening stimuli, such as health threat, so that it regularly occurs in both high- and low-anxious people. Prior studies that reported correlations between IB and pain anxiety did not include actual confrontation with pain in their paradigms [7–10]. Hence, the threat value of the stimuli was smaller and less controlled in the latter studies compared to the present one. Taken together, this could suggest that pain anxiety may influence IB in relatively safe situations but not in actual threat situations. In line with this high anxious, but not low anxious, subjects would tend to negatively interpret ambiguous health-related stimuli even when there is no imminent threat. Yet, as the threat meaning of the word stimuli becomes personally relevant, the effects of trait anxiety on IB seem to decrease. However, given that fear of ES did correlate positively with IB on expectancy ratings it is also possible that state anxiety elicited by health threat overruled the effects of trait anxiety. To explore these possibilities, an interesting venue for

future studies is to directly compare IB in threat versus safe situations in healthy people.

To our knowledge, this study is the first to employ an IB paradigm with actual pain threat and offers a number of strengths over the variety of tasks used in the current literature on IB towards (ambiguous) health-threat stimuli. First, installing imminent threat of pain via a conditioning procedure with individually adjusted painful stimuli allows studying IB in function of fear of pain more directly. Hence, this approach is not hindered by overall low levels of fear of pain in healthy participants, as frequently reported in other studies that aim to examine IB in the context of pain in healthy samples (e.g. [7, 9, 48]). Second, in contrast to other associative learning paradigms like the incidental learning task [6, 7, 49], the present paradigm does not show such large variations in learning between individuals. Our conditioning paradigm rather seems to have promoted learning, possibly due to pain threat through which our stimuli had informative value and personal relevance. Next, using a conditioning approach with painful stimuli has ecological validity over tasks that employ abstract word stimuli or pictorial stimuli only, and mirror the situation of chronic pain patients better. Last, prior studies on IB often derived the bias from either a direct interpretation of verbal ambiguity, which may be prone to social desirability, or from reaction latencies to threat-irrelevant task features, which bears the risk of being affected by factors like literacy, motor responses, or executive functioning [12]. One way to overcome these shortcomings is to include psychophysiological indexes of IB, like ERPs or eye blink reflex in response to ambiguous (threat) stimuli [20, 21, 50]. The current study combined the assessment of explicit, direct expectancy ratings with implicit, indirect startle responses for the assessment of IB, thereby allowing examining potential differential findings between these two IB indexes.

Besides these strengths, this study also has several limitations that require attention. First, participants showed overall fairly low levels and low variability in

pain anxiety which hampers detecting an association between IB and trait pain anxiety levels. Hence, future studies should consider preselecting high and low-anxious subjects. Second, a *post hoc* power analyses showed that the study was sufficiently powered to detect IB effects, but not to detect correlations between IB and anxiety constructs. In order to detect small to medium size magnitude of associations, a sample of 60–80 participants would have been necessary. Insufficient power might explain why, whilst the correlation coefficient for FPQ with IB was comparable in magnitude to other studies, it failed to reach significance here. Consequently, we cannot draw any firm conclusions from the absence of significant correlations between anxiety constructs and IB. Moreover, it needs to be mentioned that although our sample was representative in many other respects, a more gender-balanced sample would have been helpful to evaluate the generalizability of results. Indeed, evidence suggests that gender affects pain perception in general and specifically IB towards health-threat stimuli [28], such that females do not only tend to have lower pain thresholds and to be less pain-tolerant than males [51] but also show a mediating effect of negative IB on the relationship between anxiety sensitivity and pain that is not apparent in men [5]. In this regard, Keogh et al. [5] reported a small effect of gender ($R^2 = 0.225$). Furthermore, the fact that HT stimuli were reinforced during the test phase but AHT stimuli were never paired with an electrocutaneous shock might bear a problem: ambiguity might have become a safety cue, signaling absence of shock. However, it was necessary to keep a reinforcement schedule during the test phase in order to avoid fear extinction [52] but future studies might consider using a lower reinforcement schedule so that safety learning becomes more difficult. Besides, the ES intensity appeared to be relatively low and the threat value, i.e. the fear of ES and the fear of pain from ES, considerably varied among participants to the extent that some participants reported no fear at all. This may imply that our threat induction was not strong enough and might explain why no significant effects on startle response were found. Lastly, the assessment of startle response during each trial and each ITI might have

caused habituation to the sound, thus eliminating potential differential startle responses between AHT and ANHT stimuli.

Taken together, the present study shows a clear IB for ambiguous health-threat stimuli in healthy participants when confronted with an actual health threat. This effect is independent of individual levels of pain anxiety. These findings add further to our understanding of IB in the domain of health psychology. Importantly, while it is impossible to disentangle the effects of pain experience and anticipation from those of anxiety on IB among pain patients, the present study design allows for this differentiation in healthy participants. Consequently, future studies on cognitive biases should consider employing a context of actual health threat in order to increase personal relevance of the stimuli and closely mimic the situation of chronic pain patients. As illness-specific biases are thought to reinforce maladaptive illness behaviors and cognitions and thus being involved in the maintenance of symptoms [53], knowledge from such studies may eventually inform us about mechanisms underlying health anxiety and the chronification of pain as well as about valuable treatment approaches such as cognitive bias modification. Therefore, more research clarifying the relationship between IB, presence of health threat, and pain anxiety in healthy people and pain patients is needed.

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Authors' statements

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Conflict of interest: The authors confirm that there are no known conflicts of interest to declare.

Informed consent: Written informed consent was obtained from each participant at the beginning of the experiment.

Ethical approval: The study protocol was approved by the local Ethics Committee of the Faculty of Psychology and Neuroscience of Maastricht University (ERCPN) and adhered to the standards of the Declaration of Helsinki.

Appendix

Table 3: Word-stimuli used in the interpretation task, displayed in the sequence as presented to participants in the acquisition phase and test phase.

Trial	Acquisition phase		Test phase			
	HT	NHT	HT	NHT	AHT	ANHT
1	Kanker			Shampoo		
2		Potlood	Kwaal			
3	Besmetting				Naald	
4		Eiland				Bank
5		Gebergte	Ziek			
6	Wond			Rots		
7		Theelepels			Temperatuur	
8	Bloed					Pool
9	Invalide		Letsel			
10		Landkaart			Opname	
11	Pijn			Versturen		
12		Trompet			Uitslag	
13	Rolstoel					Peer
14		Ovaal		Pantalon		
15		Hoed	Dood			
16	Kramp					Bal
17		Theelepels	Blessure			
18	Rolstoel				Lam	
19		Hoed				Surfen
20	Bloed			Woordenboek		
21	Kramp				Gebrek	
22		Eiland		Komeet		
23	Kanker		Tumor			
24		Landkaart				Net
25		Potlood		Gebouw		
26	Besmetting		Ambulance			
27		Gebergte			Zweren	
28	Invalide			Slagboom		
29		Trompet	Onwel			
30	Pijn					Band
31		Ovaal			Thermometer	
32	Wond			Palm		

HT = non-ambiguous health-threat word-stimuli; NHT = non-ambiguous non health-threat word-stimuli; AHT = ambiguous health-threat word-stimuli; ANHT = ambiguous non health-threat word-stimuli.

Table 4: Translation of Dutch word-stimuli used in the interpretation task, displayed in the sequence as presented to participants in the acquisition phase and test phase.

Trial	Acquisition phase		Test phase			
	HT	NHT	HT	NHT	AHT	ANHT
1	Cancer			Shampoo		
2		Pencil	Suffering			
3	Contamination				Needle	
4		Island				Bank
5		Mountain	Ill			
6	Wound			Rock		
7		Tea spoon			Temperature	
8	Blood					Pool
9	Invalid		Lesion			
10		Map			Intake (or recording)	
11	Pain			Send		
12		Trumpet			Rash (or result)	
13	Wheelchair					Pear
14		Oval		Trousers		
15		Hat	Dead			
16	Cramp					Ball
17		Tea spoon	Injury			
18	Wheelchair				Lame	
19		Hat				Surfing
20	Blood			Dictionary		
21	Cramp				Disability (or shortage)	
22		Island		Comet		
23	Canker		Tumor			
24		Map				Net
25		Pencil		Building		
26	Contamination		Ambulance			
27		Mountain range			Sore (or pledging)	
28	Invalid			Barrier		
29		Trumpet	Unwell			
30	Pain					Band
31		Oval			Thermometer	
32	Wound			Palm-tree		

HT=non-ambiguous health-threat word-stimuli; NHT=non-ambiguous non health-threat word-stimuli; AHT=ambiguous health-threat word-stimuli; ANHT=ambiguous non health-threat word-stimuli.

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